

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

1. (currently amended) A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

- (a) ~~contacting~~ exposing an acid sphingomyelinase-deficient cell, in the presence of ~~with~~ a test compound, to a chemotherapeutic agent;
- (b) ~~exposing the cell to a chemotherapeutic agent for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity;~~
- (e) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the chemotherapeutic agent ~~for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity;~~ and
- (d) (c) monitoring the exposed cells of steps (b) (a) and (e) (b) for the presence of an apoptotic morphology,

such that if the cell from step (b) (a) exhibits a more severe apoptotic morphology, than that of the cell from step (e) (b) the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

2. (currently amended) A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

- (a) ~~contacting~~ exposing an acid sphingomyelinase-deficient cell, in the presence of ~~with~~ a test compound, to a chemotherapeutic agent;
- (b) ~~exposing the cell to a chemotherapeutic agent;~~
- (e) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the chemotherapeutic agent; and
- (d) (c) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step (b) (a) to the levels present in the exposed cell of step (e) (b),

such that if the level of sphingomyelin in the cell of step (b) (a) is less than that of the cell of step (e) (b), or the level of ceramide in the cell of step (b) (a) is greater than that of the

cell in step ~~(e)~~ (b), the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

3. (previously presented) The method of Claim 1 or 2 wherein the acid sphingomyelinase-deficient cell is part of a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene.

4. (canceled)

5. (currently amended) A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

- (a) ~~contacting~~ exposing a cell exhibiting acid sphingomyelinase activity, in the presence of with a test compound, to a chemotherapeutic agent;
- (b) ~~exposing the cell to a chemotherapeutic agent;~~
- (c) exposing a cell exhibiting acid sphingomyelinase activity to the chemotherapeutic agent, in the absence of the test compound; and
- ~~(d)~~ (c) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step ~~(b)~~ (a) to the levels present in the exposed cell of step ~~(c)~~ (b),

such that if the level of sphingomyelin in the cell of step ~~(b)~~ (a) is greater than that of the cell of step ~~(c)~~ (b), or the level of ceramide in the cell of step ~~(b)~~ (a) is less than that of the cell in step ~~(c)~~ (b), the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

6. (canceled)

7. (currently amended) The method of Claim ~~12~~ 5 wherein the cell is part of a genetically engineered nonhuman animal deficient in endogenous acid sphingomyelinase gene activity and containing integrated in its cells a functional human acid sphingomyelinase transgene capable of expressing functional human acid sphingomyelinase.

8. (canceled)

9. (currently amended) The method of Claim 1 ~~or 10~~ wherein the apoptotic morphology comprises cellular condensation, nuclear condensation or ~~zei~~ sis.

10. (previously presented) A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:
- (a) exposing acid sphingomyelinase-deficient cells, wherein the cells are part of cell lines or a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene, in the presence or the absence of a test compound, to a chemotherapeutic agent for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and
 - (b) monitoring the exposed cells of step (a) for the presence of an apoptotic morphology, such that if the cells treated with the test compound exhibit a more severe apoptotic morphology than that of the cells not treated with the test compound, the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

11. (previously presented) A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:
- (a) exposing acid sphingomyelinase-deficient cells, wherein the cells are part of cell lines or a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene, in the presence or the absence of a test compound, to a chemotherapeutic agent for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and
 - (b) comparing the levels of sphingomyelin and ceramide present in cells treated with test compound to cells untreated with the test compound, such that if the level of sphingomyelin in the cells treated with the test compound is less than that of cells not treated with the test compound, or the level of ceramide in cells treated with the test compound is greater than in cells not treated with the test compound, the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

12. (previously presented) A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising,

- (a) exposing transgenic cells, comprised of cells deficient in endogenous acid sphingomyelinase gene activity that contain a functional human acid sphingomyelinase gene capable of expressing functional human acid sphingomyelinase, to a chemotherapeutic agent in the presence or absence of a test compound; and
- (b) comparing the levels of sphingomyelin and ceramide present in cells treated with test compound to cells not treated with the test compound, such that if the level of sphingomyelin in cells treated with the test compound is greater than in cells not treated with the test compound, or the level of ceramide in cells treated with the test compound is less than that of cells not treated with the test compound, the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

13. (previously presented) A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising,

- (a) exposing cells, wherein the cells are genetically engineered cells that exhibit a greater level of acid sphingomyelinase activity than non-genetically engineered cells of the same type, to a chemotherapeutic agent in the presence or absence of a test compound; and
- (b) comparing the levels of sphingomyelin and ceramide present in cells treated with the test compound to cells not treated with the test compound, such that if the level of sphingomyelin in cells treated with the test compound is greater than in cells not treated with the test compound, or the level of ceramide in cells treated with the test compound is less than that of cells not treated with test compound, the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.